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Metformin as a new option in the medical management of breast fibroadenoma; a randomized clinical trial

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Abstract

Background: Fibroadenoma (FA) is the most common benign solid breast mass in women, with no definite method of management. Because fibroadenoma is dependent on female sex hormones and comprises hypertrophic changes at cellular levels, we investigated the effects of metformin (MF), a safe hypoglycemic agent with anti-estrogenic and anti-proliferative properties, in the management of fibroadenoma.

Methods: In this randomized clinical trial study, eligible women with fibroadenomas were assigned randomly to the metformin (1000 mg daily for six months) or the placebo group. Breast physical and ultrasound exam was performed before and after the intervention, and the changes in the size of fibroadenomas were compared in the two groups.

Results: Overall, 83 patients in the treatment, and 92 in the placebo group completed the study. A statistically significant difference in changing size between the two groups was observed only in the smallest mass. In the largest FAs, the rate of size reduction was higher in the treatment group (60.2 % vs. 43.5 %); while a higher rate of enlargement was observed in the placebo group (38 % vs. 20.5 %). In the smallest FAs, the rate of the masses that got smaller or remained stable was about 90 % in the treatment group and 50 % in the placebo group. We categorized size changes of FAs into < 20 % enlargement and \geq 20 % enlargement. The odds ratio (OR) for an enlargement less than 20% was 1.48 (95 % CI = 1.10–1.99) in the treatment group in comparison with the placebo group; the odds for an enlargement less than 20% was higher in women with multiples fibroadenomas (OR = 4.67, 95 % CI: 1.34–16.28). In our study, no serious adverse effect was recorded, and the medicine was well-tolerated by all users.

Conclusions: This is the first study that evaluates the effect of MF on the management of fibroadenoma, and the results suggest a favorable effect. Larger studies using higher doses of MF and including a separate design for patients with single or multiple FAs are suggested in order to confirm this effect.

Trial registration: This trial (IRCT20100706004329N7) was retrospectively registered on 2018-10-07.

Keywords: Fibroadenoma, Fibrocystic Breast Disease, Breast Ultrasonography, Metformin, Therapy

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Declarations

Ethics approval and consent to participate

The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran approved the study (Approval ID: IR.TUMS.VCR.1397.357). All participants read and signed a written informed consent before entering the study.

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interest to declare.

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References

- Smith G, Burrows P. Ultrasound diagnosis of fibroadenoma-is biopsy always necessary? *Clin Radiol*. 2008;63(5):511–5.
- Coriaty Nelson Z, Ray RM, Gao DL, Thomas DB. Risk factors for fibroadenoma in a cohort of female textile workers in Shanghai, China. *Am J Epidemiol*. 2002;156(7):599–605.
- Li JJ, Gary MT. Core needle biopsy diagnosis of fibroepithelial lesions of the breast: a diagnostic challenge. *Pathology*. 2020; 52(6):627–34.
- Kuijper A, Mommers EC, van der Wall E, van Diest PJ. Histopathology of fibroadenoma of the breast. *Am J Clin Pathol*. 2001;115(5):736–42.
- Levi F, Randimiron L, Te VC, la Vecchia C. Incidence of breast cancer in women with fibroadenoma. *Int J Cancer*. 1994;57(5):681–3.
- Chae YK, Arya A, Malecek MK, Shin DS, Carneiro B, Chandra S, et al. Repurposing metformin for cancer treatment: current clinical studies. *Oncotarget*. 2016;7(26):40767–80.
- Tejwani PL, Nerkar H, Dhar A, Kataria K, Hari S, Thulker S, et al. Regression of fibroadenomas with centchroman: a randomized controlled trial. *Indian J Surg*. 2015;77(2):484–9.
- Dialani V, Chansakul T, Lai KC, Kilmore H, Sayegh NY, Slanetz PJ. Enlarging biopsy-proven fibroadenoma: Is surgical excision necessary? *Clin Imaging*. 2019;57:35–9.
- Gordon PB, Gagnon FA, Lanzkowsky L. Solid breast masses diagnosed as fibroadenoma at fine-needle aspiration biopsy: acceptable rates of growth at long-term follow-up. *Radiology*. 2003;229(1):233–8.
- Olfatbakhsh A. Clinical Guidelines for Diseases of the Breast. Breast Cancer Research Center, Motamed Cancer Institute. Tehran, Iran. 2019: Page 19. Available at: <https://bdc.tums.ac.ir/uploads/140/2020/Jun/20/ICBC%20protocol%201398.pdf>. Accessed on 3 Apr 2021.
- Hanley JA, Negassa A, Edwards MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol*. 2003;157(4):364–75.
- Grady I, Gorsuch H, Wilburn-Bailey S. Long-term outcome of benign fibroadenomas treated by ultrasound-guided percutaneous excision. *Breast J*. 2008;14(3):275–8.
- Waleed Y, Mohamed AS, Ahmed AD, Magdy M. Endoscopic Resection of Breast Fibroadenoma. *Med J Cairo Univ*. 2018;86:2861–9.
- Dowlatshahi K, Wadhwani S, Alvarado R, Valadez C, Dieschbourg J. Interstitial Laser Therapy of Breast Fibroadenomas With 6 and 8 Year Follow-Up. *Breast J*. 2010;16(1):73–6.
- Yang BR, Kim HJ, Shin KM, Cho SH, Jang Y-J, Lee HJ, et al. Serial Ultrasound Findings After Laser Ablation for Benign Breast Lesions on Long-Term Follow-Up: Implications for Evaluation of Procedural Success. *Photomed Laser Surg*. 2015;33(8):404–8.
- Li P, Xiao-Yin T, Cui D, Chi J-c, Wang Z, Wang T, et al. Evaluation of the safety and efficacy of percutaneous radiofrequency ablation for treating multiple breast fibroadenoma. *J Cancer Res The*. 2016;12(7):138–42.
- Brenin DR, Patrie J, Nguyen J, Rochman CM. Treatment of breast fibroadenoma with ultrasound-guided high-intensity focused ultrasound ablation: a feasibility study. *J Breast Imaging*. 2019;1(4):316–23.
- Dixon J, Dobie V, Lamb J, Walsh J, Chetty U. Assessment of the acceptability of conservative management of fibroadenoma of the breast. *Br J Surg*. 1996;83(2):264–5.
- Wilkinson S, Anderson T, Rifkind E, Chetty U, Forrest A. Fibroadenoma of the breast: a follow-up of conservative management. *Br J Surg*. 1989;76(4):390–1.
- Bayles B, Usatine R. Evening primrose oil. *Am Fam Physician*. 2009;80(12):1405–8.
- Kollias J, Macmillan R, Sibbering D, Burrell H, Robertson J. Effect of evening primrose oil on clinically diagnosed fibroadenomas. *Breast*. 2000;9(1):35–6.
- Tan-Chiu E, Wang J, Costantino JP, Paik S, Butch C, Wickerham DL, et al. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. *J Natl Cancer Inst*. 2003;95(4):302–7.
- Viviani R, Gebrim L, Baracat E, De GL. Evaluation of the ultrasonographic volume of breast fibroadenomas in women treated with tamoxifen. *Minerva Ginecologica*. 2002;54(6):531–5.
- Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. *World J Surg*. 2007;31(6):1180–6.
- Gupta N. A Prospective Study to study the Efficacy and Side Effects of Ormeloxifene in Regression of Mastalgia and Fibroadenoma: Is It the Ideal Drug? *SAFGO*. 2016;8(1):48–56.
- Roy SB, Hembram R. A comparative study of efficacy of centchroman and evening primrose oil in treatment of benign breast disease. *J Evol Med Dent Sci*. 2018;7(31):3518–25.
- Buckley MM-T, Goa KL. Tamoxifen. *Drugs*. 1989;37(4):451–90.
- Ellis AJ, Hendrick VM, Williams R, Komm BS. Selective estrogen receptor modulators in clinical practice: a safety overview. *Expert Opin Drug Saf*. 2015;14(6):921–34.
- Heckman-Stoddard BM, Gandini S, Puntoni M, Dunn BK, DeCensi A, Szabo E, editors. Repurposing old drugs to chemoprevention: the case of metformin. *Semin Oncol*. 2016; 43(1):123 – 33.
- Shurab NT, Arafa E-SA. Metformin: A review of its therapeutic efficacy and adverse effects. *Obes Med*. 2020;17:100186.
- Huiart L, Dell'Aniello S, Suissa S. Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. *Br J Cancer*. 2011;104(10):1558–63.
- Zeidan B, Anderson K, Peiris L, Rainsbury D, Laws S. The impact of tamoxifen brand switch on side effects and patient compliance in hormone receptor positive breast cancer patients. *Breast*. 2016;29:62–7.
- Roshan MH, Shing YK, Pace NP. Metformin as an adjuvant in breast cancer treatment. *SAGE Open Med*. 2019;7:2050312119865114.
- Alimova IN, Liu B, Fan Z, Edgerton SM, Dillon T, Lind SE, Thor AD. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. *Cell Cycle*. 2009;8(6):909–15.
- Lord SR, Cheng WC, Liu D, Gaude E, Haider S, Metcalf T, Patel N, Teoh EJ, Gleeson F, Bradley K, Wigfield S. Integrated pharmacodynamic analysis identifies two metabolic adaption pathways to metformin in breast cancer. *Cell Metab*. 2018;28(5):679–88.
- Hadad SM, Hardie DG, Appleyard V, Thompson AM. Effects of metformin on breast cancer cell proliferation, the AMPK pathway and the cell cycle. *Clin Transl Oncol*. 2014;16(8):746–52.
- Rice S, Pellat L, Ahmetaga A, Bano G, Mason HD, Whitehead SA. Dual effect of metformin on growth inhibition and oestradiol production in breast cancer cells. *Int J Mol Med*. 2015;35(4):1088–94.
- Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod*. 2002;17(11):2858–64.
- Løvkvik TS, Carlsen SM, Salvesen Ø, Steffensen B, Bixo M, Gómez-Real F, et al. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(4):256–66.
- Talaei A, Moradi A, Rafiei F. The evaluation of the effect of metformin on breast fibrocystic disease. *Breast Dis*. 2017;37(2):49–53.

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